Prediction Model of Pregnancy Outcomes in Artificial Insemination with Donor Cycles

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INTRODUCTION

Theoretically, normal fertile women seeking artificial insemination with donor (AID) in natural cycles do not differ from naturally conceiving couples, except for the advantage of implementing IUI. Hence, it is expected that donor insemination in natural cycles of fertile women would yield at least similar results compared to natural reproduction. Multiple studies evaluated the predictive factors influencing AID outcomes including female age, ovarian stimulation protocols, BMI, smoking, number of unsuccessful cycles and sperm parameters. Inconsistent results were reported regarding the effect of ovarian stimulation and total motile sperm (TMS) on the success rates of AID. While some studies showed that ovarian stimulation with gonadotropins and higher TMS significantly increase pregnancy rates, others didn't find a significant effect of these variables.

HYPOTHESIS

Female patients undergoing AID with no known infertility problem might not benefit from superovulation, and success rates might not be affected by the TMS.

OBJECTIVES

- Primary objective is to compare the clinical pregnancy rate between different levels of TMS in AID cycles divided into 8 groups
- Secondary objective is to compare the clinical pregnancy rate between 4 different ovulation induction protocols in AID cycles

METHODS

Patients who underwent artificial insemination with donor (AID) cycles at the university affiliated fertility center-OVO clinic in Montreal, Canada from 2011 to 2015 were selected. A total number of 4333 AID cycles were performed during this period of time corresponding to 1179 patients, resulting in 744 positive pregnancy tests. Data was retrospectively retrieved. Potential predictive factors of pregnancy were collected, including female age at the time of insemination, smoking status, Body Mass Index (BMI), length of menstrual cycle, AMH level, 14 sperm-related factors before and after wash, TMS divided into 8 groups (<0.5M, [0.5-1[, [1-5[, [5-10[, [10-20[, [20-40[, [40-80[, ≥80M), number of previous unsuccessful attempts of insemination cycles, number of previous successful attempts of insemination cycles resulting in a clinical pregnancy, treatment variables (gonadotropin stimulation, oral medication for ovulation induction, natural cycle, combination of oral medications and gonadotropin stimulation) and the use of hCG ovulation trigger versus urinary ovulation monitoring.

- Inclusion criteria
  - AID cycle
- Exclusion criteria
  - Uterine factor infertility
  - Tubal factor infertility
  - Recurrent pregnancy losses
  - Abnormal hormonal profile (TSH, Prolactin)

Data management was performed using Matlab software.

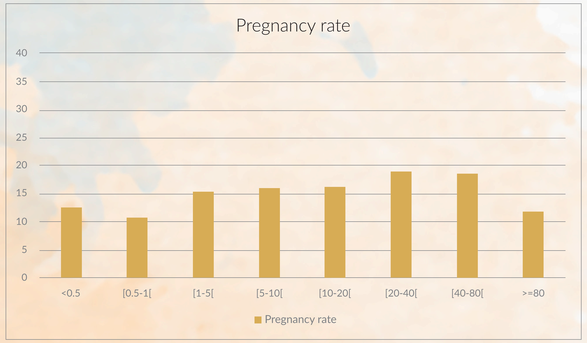

FIGURE 1. COMPARISON OF CLINICAL PREGNANCY RATES BY THE TMS LEVEL IN MILLION.

TABLE 1 – DEMOGRAPHIC AND CYCLE CHARACTERISTICS

	<0.5	[0.5-1[	[1-5[	[5-10[	[10-20[	[20-40[	[40-80[	≥80	Total	P value
Age (years)	36.5 ± 6.1	34.2 ± 4.9	34.4 ± 4.9	34.9 ± 4.7	34.8 ± 4.9	34.9 ± 4.7	35.4 ± 4.6	37 ± 3.8	34.8 ± 4.8	NS
BMI (Kg/m2)	25.5 ± 4.9	27.3 ± 4.4	28.4 ± 7.5	27.9 ± 6.1	26.6 ± 5.7	26.7 ± 6.2	26.4 ± 6.2	26 ± 4	27 ± 6.3	NS
AMH (ng/ml)	0.74 ± 1	1.8 ± 1.5	2 ± 2	2.2 ± 2.4	2.2 ± 2	2.4 ± 2.3	2 ± 1.7	1.6 ± 1.5	2.2 ± 2.2	NS
Menstrual cycle (days)	27.3 ± 3.6	28.9 ± 3.1	28.7 ± 2.5	29.2 ± 6.5	29 ± 3.9	28.8 ± 3.7	29.3 ± 7	28.4 ± 1.7	28.9 ± 4.4	NS
Endometrial thickness (mm)	8.5 ± 1.5	7.6 ± 1.6	8.2 + 2.1	8.2 ± 2.1	8.1 ± 2.1	8.1 ± 2.5	8 ± 1.8	7.5 ± 1.5	8.1 ± 2.2	NS
Follicles ≥ 14mm	2.5 ± 0.7	1.7 ± 0.9	1.6 ± 1	1.7 ± 0.9	1.7 ± 1.1	1.6 ± 0.8	1.6 ± 0.9	1.7 ± 0.9	1.7 ± 1	NS
Previous IUI	3 ± 3	2.9 ± 2.7	3 ± 3	2.9 ± 2.7	3 ± 2.6	3.1 ± 2.8	3.3 ± 3.2	2.8 ± 2.4	3 ± 2.8	NS
Previous failed AID	3 ± 3	2.7 ± 2.7	2.8 ± 3	2.7 ± 2.7	2.8 ± 2.6	2.9 ± 2.8	3.1 ± 3	2.6 ± 2.4	2.8 ± 2.8	NS
Previous Successful AID	0 ± 0	0.1 ± 0.4	0.1 ± 0.4	0.2 ± 0.5	0.3 ± 0.5	0.2 ± 0.5	0.3 ± 0.6	0.1 ± 0.3	0.2 ± 0.5	NS
Indication										
Single patient	57%	42%	44%	45%	40%	39%	37%	31%	44%	NS
Homosexual female couple	14%	38%	31%	34%	38%	37%	43%	50%	35%	NS
Male factor	29%	20%	25%	21%	22%	24%	20%	19%	21%	NS
Smoking status										
Smoker	0%	19%	10%	8%	8%	10%	7%	7%	10%	NS
Non-smoker	100%	81%	90%	92%	92%	90%	93%	93%	90%	NS
Protocol										
Gn	0%	0%	0.8%	0.5%	0.7%	0.4%	0%	0%	0.2%	NS
Oral	62%	61%	55%	54%	60%	57%	54%	41%	56%	NS
Natural	25%	29%	34%	32%	28%	29%	31%	35%	30%	NS
Oral + Gn	13%	10%	10%	13%	11%	14%	15%	24%	14%	NS
hCG trigger										
Yes	100%	85%	90%	86%	83%	84%	80%	75%	84%	NS
No	0%	15%	10%	14%	17%	16%	20%	25%	16%	NS

TABLE 2 – REPRODUCTIVE OUTCOMES FOR THE DIFFERENT GROUPS OF TMS

	<0.5 (n=8)	[0.5-1[(n=28)	[1-5[(n=625)	[5-10[(n=530)	[10-20[(n=1234)	[20-40[(n=1502)	[40-80[(n=389)	≥80 (n=17)	P value
Clinical pregnancy	12.5%	10.7%	15.3%	16%	16.2%	19%	18.5%	11.7%	NS
Miscarriage	0%	30.3%	17.7%	20%	17.5%	23.4%	16.6%	0%	NS
Multiple gestation	0%	0%	3.8%	3.4%	8.8%	6.2%	6.2%	50%	NS

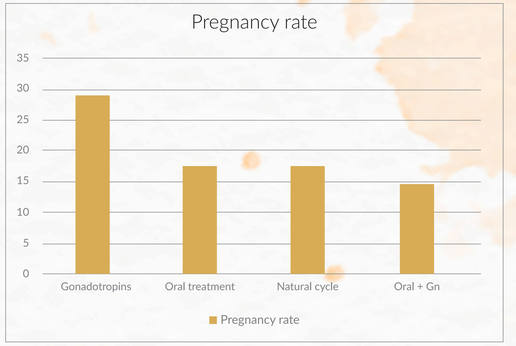

FIGURE 2. COMPARISON OF CLINICAL PREGNANCY RATE BY THE PROTOCOL OF OVULATION INDUCTION

RESULTS

Regarding the demographic and cycle characteristics, no difference was noted when comparing all 8 groups of TMS (Table 1) . The lowest clinical pregnancy rate was 10.7% for the group 2 TMS = ([0.5-1[M), while the highest rate was 19.0% for the group 6 TMS = ([20-40[M (Figure 1). No difference is noted when comparing the clinical pregnancy, multiple gestation, miscarriage and rates for the TMS groups altogether (Table 2). However, when taking TMS= ([10-20[M) as a control, no statistical difference was noted for all the other levels of TMS except for group 6 that has the highest clinical pregnancy rate (p=0.005) (Figure 1).

As for the ovulation induction protocols, the highest clinical pregnancy rate was noted with gonadotropins only protocol reaching 29.1%. Interestingly, natural cycle was as good as oral ovulation induction yielding a clinical pregnancy rate of 17.4% (Figure 2). When comparing all groups of ovulation induction, no difference is noted for all the reproductive outcomes. However, the only statistically different result was detected when comparing the outcome of each ovulation induction group with the gonadotropins group showing a higher clinical pregnancy: in the latter.

DISCUSSION

Our results are consistent with many studies in the literature regarding the effect of TMS and ovulation induction protocols on the reproductive outcomes in IUI cycles. We collected data from donor insemination cycles in female patients with no diagnosis of infertility. This study shows that even low levels of TMS and in natural cycles, AID is always effective and yields similar results to other protocols of ovulation induction and higher levels of TMS. It is reasonable hence to consider decreasing the burden of medication and to accept lower levels of TMS in AID cycles. This conclusion cannot be generalized to patients with a history of unexplained or female factor infertility, who represents different populations to the one evaluated in our study.

One major limitation of this study is the retrospective design. However no difference was noted between the groups when it comes to the demographic and cycle characteristics. To control for potentially confounding variables, a multivariate regression analysis will be performed in the final statistical analysis.

In order to give better prediction of the chances of pregnancy in AID cycles we will generate in a second step a predictive model. To prevent overfitting of the predictive model, the data will be randomly divided into two samples: 70% of all cycles will be used for the primary analyses (training set, n= 3033) and 30% of cycles will be used for internal model validation (validation set; n= 1300).. The predictive model will be developed with the use of backward selection method which consists of entering the independent variables into the equation first and each factor is then deleted one at a time if they do not contribute to the regression equation. As a result the significant variables will be included in our predictive model.

CONCLUSION

TMS level and ovulation induction protocol does not seem to affect the clinical outcomes of AID cycles with no infertility diagnosis. Natural cycle is a reasonable option for these patients. Low levels of TMS even below 0.5 M should not be considered as an indication to cancel AID cycles.

Fertility Preservation Outcome in Breast and Non-Breast Cancer Patients

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Introduction:
The purpose of our study is to evaluate and compare the fertility preservation outcomes including pregnancy and livebirth in breast and non-breast cancer patients

Material and Methods:
A retrospective cohort study conducted at a single fertility center from 2009 -2020 included all cancer patients at age ≤40 at time of IVF-fertility preservation (n=336).**Primary outcome:** number of frozen eggs and embryos. **Secondary outcome**: Pregnancy and live birth.

Results:

- ✓ A total of 336 patients underwent IVF-fertility preservation, 123 patients had breast cancer and 213 patients with other non-breast cancers.
- ✓ Breast cancer patients were significantly older than non-breast cancer patients (32.85 vs 27.6-year, P <0.0001), AFC (14.85 vs 16.15 follicle, P=0.237) , FSH level (7.33 vs 8.16 mg/dL, P= 0.738), total gonadotrophin dose (2733 IU vs 2428 IU , P=0.332) and days of stimulation (5.55 vs 6.04 days, P=0.351) were similar in both groups.
- ✓ In terms of reproductive response, there were no significant different between breast and non-breast cancer patients in the total number of eggs retrieved (13.14 vs 13.3, P= 0.860), the number of MII oocytes (8.64 vs 8.7, P=0.928) and the number of cryopreserved oocytes (8.84 vs 10.18 ,P=0.225).
- ✓ The number of cryopreserved embryos were higher among breast cancer patients (3.72 vs 2.25, P=0.017).
- ✓ Out of the 336, follow up data was available for 198 (58.9%) patients with a mean follow up of 3.2 years.
- ✓ Among the 198 patients for whom data was available, 61 patients had breast cancer and 135 had other non-breast cancers.
- ✓ Overall ,40 patients became pregnant. Of these 35% (n=14) had breast cancer and 65% (n=26) had other non breast cancers.
- ✓ Among patients who returned to use their stored materials, 23 patients underwent FET cycles. Of the 23 patients , 70% (n=16) achieved a pregnancy and 63% (n=10) achieved at least one live birth.

Conclusions:
Breast cancer patient were older than non-breast cancer at time of fertility preservation but with comparable reproductive response.
Cryopreserved embryos were higher among breast than non-breast cancer patient(3.72 vs 2.25, P=0.017). Of those who returned to use their cryopreserved reproductive materials, ≥60 % achieved pregnancy in both breast cancer and in non-breast cancers.

Table 1: demography and baseline ovarian reserve among breast and non-breast cancer

	Breast cancer (n=123)	Non-breast cancer (n=213)	P- value
Age at time FP	32.85	27.6	<0.0001
AFC	14.85	16.15	0.237
FSH in mg/dl	7.33	8.16	0.738
Total dose of gonadotropin IU	2733	2428	0.332
Stimulation period in day	5.55	6.04	0.351

Table 2: Ovarian stimulation response among breast and non-breast cancer

	Breast cancer (n=123)	Non-breast cancer (n=213)	P- value
Total number of oocyte retrieval	13.14	13.3	0.860
Number of Mature oocytes MII	8.64	8.7	0.928
Number of cryopreserved oocytes	8.84	10.18	0.225
Number of cryopreserved embryos	3.72	2.25	0.017

Table 3: Pregnancy and livebirth among breast and non-breast cancer

	Breast cancer (n=123)	Non-breast cancer (n=213)
No. of returned for follow up	61	135
No. of patients pregnant	14	26
No. of pregnancies	21	37
No. of livebirths	11	22
No. of patients who did FET	10	13
No. of patients with FET pregnancy	6	10
No. of patients with livebirth after FET	3	7

Impact of protocol adjustments due to the Covid-19 Pandemic on infertility treatment for IVF and FET outcomes

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The Covid-19 pandemic resulted in many adjustments to patient care protocols including fewer: i) patient visits; ii) ultrasound scans; iii) laboratory investigations and iv) face-to-face interaction.

OBJECTIVE:

To evaluate and compare pregnancy rates among patients who had IVF and frozen embryo transfer (FET) pre-pandemic and during the Covid-19 pandemic

MATERIALS AND METHODS:

Patients who underwent IVF and FET were divided into either the:

Pre-pandemic group (FET n=260 and IVF n=226; treated between June 2019 – December 2019); or

Pandemic group (FET n=318 and IVF n=224; treated between June 2020 – December 2020).

The primary outcome was clinical PR, defined as the presence of a gestational sac at ultrasound examination.

Statistical analysis was performed and reported as mean ± standard deviation of the mean. T-test and Classical Chi-square calculations where appropriate was conducted to determine significance ($P < 0.05$) between groups.

RESULTS:

Clinical PR (**43.5%** vs. **46.9%**) and PR (**55.8%** vs **57.5%**) were not statistically different between the pre-pandemic and pandemic group of patients who had FET.

Table 1: Comparison of cycle characteristics between groups.

IVF comparison	Pre-pandemic n=226		Pandemic n=224		Statistics	
Description	mean	SD	mean	SD	t-test	p < 0.05
Age	34.3	6.2	35.3	4.6	**0.04**	S
TotalDoseFSH	3694.8	1824.0	3642.1	1728.7	0.75	NS
# Stim Days	10.0	1.0	12.0	1.0	0.53	NS
E2 Level	9511.2	5365.6	10949.3	6369.3	**0.01**	S
Day of Hcg	13.5	2.1	13.4	1.7	0.62	NS
Retrieved	11.4	6.7	12.0	7.1	0.34	NS
Injected	8.3	5.1	9.5	5.6	**0.02**	S
Ferilitization rate	77.0	26.3	82.6	20.5	**0.01**	S
CleavedEmbryos	6.4	4.3	7.5	4.7	**0.01**	S
Utilization (blast) rate	31.8	65.4	36.1	22.6	0.18	NS
BMI	25.8	5.8	25.8	5.3	0.35	NS
Duration of infertility	1.8	1.3	2.2	1.6	0.12	NS
AMH	14.0	10.3	16.5	12.6	0.46	NS

CONCLUSION:

Treatment protocol adjustments due to Covid-19 did not adversely affect FET outcomes. Interestingly, fertilization rate was better and the number of cleaved embryos were higher in patients who had IVF treatment during pandemic.

It is reassuring to know the pandemic protocol adjustments did not have a negative impact on IVF and FET outcomes in our clinic.

Miniaturizing and Semi-Automating the Manual Clinical VeriSeq-PGT-A MiSeq Library Preparation Protocol Using Mosquito®HV.

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INTRODUCTION

- Next generation sequencing (NGS) is a reliable technique used in the CReATe Reproductive Genetics Lab for clinical sequencing of embryonic DNA.
- NGS is used for the previously validated VeriSeq PGT-A library preparation protocol[1].
- While manual library protocol produces reliable results, it is time-consuming, labor-intensive and can become costly.
- Since the implementation of the government-funded single cycle of IVF, CReATe has seen a large increase in number of patients, as well as in number of embryos, per month.
- It was therefore important to miniaturize and semi-automate the VeriSeq PGT-A library preparation protocol in order to keep up with this increase.

OBJECTIVES

- To increase the number of samples tested in a single NGS library preparation.
- To reduce chances of technical error, variability, turn-around time and manual labor.
- To decrease cost by reducing reagent/material consumption.

MATERIALS AND METHODS

Parallel Runs

- The samples used in this study were from patients undergoing PGT-A/M at CReATe Fertility Centre.
- We performed PGT-A on 72 embryos following the VeriSeq-PGT-A protocol, using:
  1) standard manual library preparation following manufacturer's protocol (5µL of WGA-DNA),
  2) the new miniaturized and semi-automated protocol using Mosquito®HV (1µL of WGA-DNA)
- We present three parallel VeriSeq library preparation runs, with manual library preparation as our control.
- Each parallel run consisted of the same 24 sample set.
- Data analysis was performed using BlueFuse software.
- Quality control (QC) measures and ploidy status were compared.

Mosquito®HV Only

- The samples used in this study were from patients undergoing PGT-A/M at CReATe Fertility Centre.
- We performed PGT-A on an additional 186 samples following the VeriSeq-PGT-A protocol, using:
  1) the new miniaturized and semi-automated protocol using Mosquito®HV (1µL of WGA-DNA)
- Eight library preparation runs were performed using only Mosquito®HV.
- The samples were multiplexed using 24-unique barcodes
- Each cohort of 24 was sequenced on MiSeq under the same conditions.
- Data analysis was performed using BlueFuse software.
- QC measures were assessed and compared to the VeriSeq PGT-A MiSeq Assessment Guide Values as reference.

RESULTS

Table 1: Time (min) needed for a 24 sample manual VeriSeq library preparation, and time needed for a 96 sample automated Mosquito®HV VeriSeq library preparation.

Method	Total Time (min)	Time (min) Per Sample	Time Saved Per Sample
Manual (24 samples)	270	11.25	72%
Mosquito®HV (96 samples)	300	3.125	

Table 2: Total price ($) per sample between a standard, 24 sample manual VeriSeq library preparation, and a 96 sample automated Mosquito®HV VeriSeq library preparation.

Method	Per Sample ($)	Cost Saved Per Sample
Manual (24 samples)	253.72	37%
Mosquito®HV (96 samples)	159	

Table 3: Concordance (%) of ploidy status between manual and Mosquito®HV in the parallel runs.

Ploidy Status	Concordance (%)
Euploid	100
Aneuploid	100
Mosaic	100
Sex	100

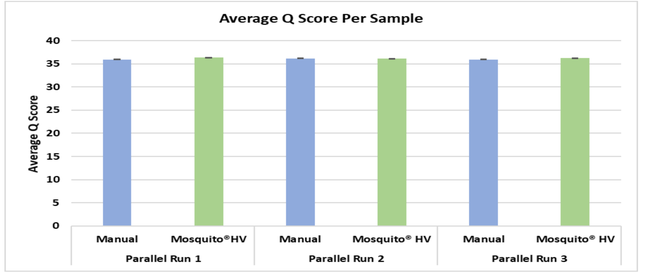

Figure 1: Average Q scores per sample for all parallel runs exceed the minimum value of 30 and the optimum value of 35.

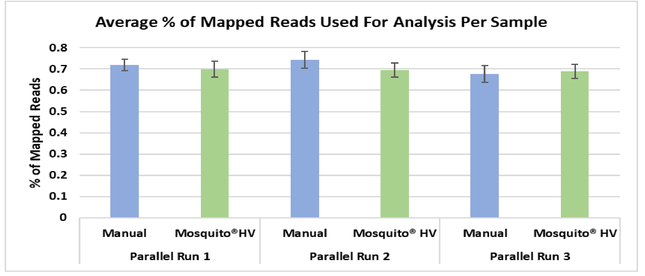

Figure 2: Average % of mapped reads used for analysis, for all three parallel runs.

Table 4: Summary of the total averages for important QC measures for all Mosquito®HV runs (186 samples), including VeriSeq PGT-A MiSeq guidelines as reference.

QC Measures	Mosquito®HV Total	VeriSeq PGT-A MiSeq Assessment Guide Values
Average Q Score	35.60	>35 (optimal) >30 (minimum)
Average Number of Total Reads	1 105 831.93	1 000 000 (optimal) 700 000 (minimum)
Average Number of Mapped Reads	933 431.10	800 000 (optimal)
Average Number of Reads After Filtering	685 388.72	600 000 (optimal) 250 000 (minimum)
Average DLR	0.18	<0.2 (optimal) <0.4 (minimum)
Average % of Mapped Reads Used for Analysis	0.73	N/A
Cluster Density (K/mm²)	1497	1200-1400 K/mm² (optimal) 1100-1600 K/mm² (minimum)

CONCLUSION

- Our findings showed, for the first time, the concordance and efficacy of using Mosquito®HV for semi-automating and miniaturizing the VeriSeq-PGT-A MiSeq library preparation protocol, when compared to the standard manually performed protocol.
- Adaptation of this new technology represents a significant advance in accuracy and efficiency for laboratories performing PGT-A/M around the world.
- Basic technical training is also required to operate Mosquito®HV successfully.

ACKNOWLEDGEMENTS

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Rekovelle and Menopur mixed protocol for controlled ovarian stimulation in IVF

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INTRODUCTION

Follitropin delta (Rekovelle) is a human recombinant FSH that is derived from a fetal retinal cell line. A dosing algorithm promoted by the manufacturer based on AMH and body weight offers comparable outcomes to a popular reference follitropin alpha protocol. However, limited data is available when considering "mixed protocols" combining the recombinant FSH product with hp-hMG (Menopur). The objective of this study was to determine whether a mixed protocol would be beneficial for the primary patient outcome of good-quality usable blastocysts. Secondary outcomes of interest included oocytes retrieved, fertilization rates, and patient safety (OHSS risk).

MATERIALS & METHODS

A total of 46 women aged 18-40, undergoing their first IVF cycle between May 2018 to November 2018 at Hannam Fertility Centre (HFC) and CCRM Toronto were included in this study. Rekovelle was dosed per the recommended algorithm, matched to a variable dose of Menopur from 75 to 225IU dependent on the Rekovelle dose. Antagonist dosing & timing, and ovulation trigger dosing & timing, were determined by the clinical team to optimize patient outcomes. Embryos were cultured to blastocysts and good-quality usable blastocysts (3BB or better as per Gardner-Schoolcraft blastocyst grading criteria) were frozen. Outcomes were compared to the ESTHER-1 trial.

CONCLUSION

Our results suggest ovarian stimulation with a mixed protocol of Rekovelle and Menopur may result in higher numbers of good-quality usable embryos compared to a Rekovelle algorithm alone. The corresponding secondary outcomes of oocytes retrieved and fertilization rate trended higher as well, while OHSS risk trended lower.

RESULTS

Table 1 – Patient demographics

	ESTHER-1 Trial	HFC Data
Characteristic	Individualized follitropin delta (n=665)	Mixed follitropin delta and human menopausal gonadotropin (n=46)
Age (y)	33.4 ± 3.9	35.5 ± 2.9
<35	394 (59.2)	18 (39.1)
35-37	161 (24.2)	16 (34.8)
38-40	110 (16.5)	12 (26.1)
Body Weight (KG)	64.7 ± 10.7	68.8 ± 16.1
Infertility History		
Duration of infertility (mo)	35.3 ± 24.4	25.3 ± 16
Primary Infertility (%)	70.7	76.0
Primary Reason for Infertility		
Unexplained	42.3	82.6
Tubal	13.8	0
Male Factor	40.3	15.2
Endometriosis I/II	3.3	2.2
Other	0.3	0
Endocrine Profile		
AMH (pmol/L)	16.3 (9.0-24.8)	17.3 (11.6-22.5)
FSH (IU/L)	7.5 (6.2-9.2)	6.7 (5.6-8.0)
E2 (pmol/L)	158 (128-199)	164 (108-182)

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RESULTS

Table 2 – Patient outcomes

	ESTHER-1 Trial	HFC Data
Outcome Variable	Individualized follitropin delta (n=665)	Mixed follitropin delta and human menopausal gonadotropin (n=46)
Oocytes Retrieved	10.0 ± 5.6	15.1 ± 7.9
Ovarian Response Stratified by AMH		
Women with AMH <15 (at risk of hypo-response) (n)	280	20
Oocytes Retrieved	8.0 ± 4.3	12.8 ± 7.1
Poor responders (≤ 4 oocytes)	33 (11.8)	0 (0)
Women with AMH ≥15 (at risk of hyper-response) (n)	355	26
Oocytes Retrieved	11.6 ± 5.9	16.9 ± 8.2
Excessive responders (≥ 15 oocytes)	99 (27.9)	15 (57.7)
Excessive responders (≥ 25 oocytes)	36 (10.1)	11 (42.3)
Fertilized oocytes (n)	5.5 ± 3.7	8.8 ± 5.6
Fertilization rate (%)	56.0 ± 24.5	76.2 ± 17.5
Blastocysts		
Good-quality usable blastocysts (n)	2.0 ± 2.2	5.0 ± 4.2
Women with blastocyst cryopreserved	402 (60.5)	43 (93.5)
Safety Outcomes		
All OHSS	23 (3.5)	0 (0)

Note: Values are mean ± SD or number (percentage), unless stated otherwise.

HOW TO DOSE REKOVELL FOR INSEMINATION ,OUR RECOMENDATIONS BASED ON OUR RETROSPECTIVE DATA

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Introduction:

Follitropin Delta(FD) is used exclusively for in-vitro fertilization(IVF). A dosing algorithm exists for IVF but is needed currently for IUI cycles. The purpose of our study is to determine dosing for FD in IUI cycles.

Material and Methods:

Retrospective study on 157 subjects conducted at a single fertility center from January 2017 to March 2020. All included patients were stimulated with FD for IUI with at least one patent fallopian tube, no intra-cavity pathology, and ≥5million total motile sperm count.

We determined the number of cycles with failed, normal or over stimulation based on the recommendations of the 2020 ASRM committee opinion for ovarian stimulation with gonadotropin in anovulation; which recommends cancelling the cycle when ≥3 follicles ≥10 mm or >2 follicles ≥16 mm, at the time of triggering. We stratified the group based on (AFC, AMH, and body weight). The traditional rate for over stimulation in COH IUI is unknown. In this study we accepted up to a 25% over stimulation rate.

Results:

Women with AFC<6; when daily doses ranged (3-12mcg), 46% stimulated correctly, 49% over stimulated, and 6% failed to stimulate.

Women with AFC<6 & daily dose 3-4 mcg , 50% failed to stimulate while when dose ranged 6-9 mcg ,45% over stimulated.

Among women with AMH≥1.5 ng/ml & FD dose 2-3mcg daily, 79% stimulated correctly, 17% over stimulated and 3.4% failed to stimulate.

Women with AMH<1.0ng/ml & dose 2-4mcg,75% stimulated correctly and 25% over-stimulated, 0% failed to stimulate.

Women with body weight ≥80kg and daily dose range (3-12mcg),58% stimulated correctly , 15% failed to stimulate and 28% over stimulated while women with body weight ≥80kg and dose was 4-6mcg 50% stimulated correctly, 25% failed to stimulate and 25% over stimulated.

Table 1: Causes of infertility among all subjects

Decrease ovarian reserve DOR	40%
Endometriosis (stage 1 or 2)	9%
Male factor	29%
PCOS	9%
Single (no partner)	2%
Unexplained	9%
Other	2%

Table 2: Ovarian stimulation response among all subjects in general and stratified

	Stimulated	Over-stimulated	Failed stimulated
Over all 157 subjects	49%	45.5%	5.6%
Serum AMH Stratified			
AMH ≥ 1.5 ng/dl			
FD dose ≤3 mcg	79%	17%	3.4%
AMH ≤ 1 ng/dl			
FD dose ≤4 mcg	75%	25%	0%
AFC Stratified			
AFC ≥ 10			
FD dose 2-12 mcg	53%	40%	8%
FD dose ≤3 mcg	73%	24%	2.4%
AFC < 6			
FD dose 3-12 mcg	46%	49%	6%
FD dose ≤ 4 mcg	-	-	50%
FD dose 6-9 mcg	-	45%	-
Body Weight Stratified			
Weight ≥80 kg			
FD dose 3-12 mcg	58%	28%	15%
FD dose 4-6 mcg	50%	25%	25%

Conclusions: In COH IUI cycle, women with AFC≥10 or AMH≥1.5 ng/ml; starting doses of FD should be 2-3mcg daily. For women with AFC<6 or AMH<1 ng/ml; starting dose should be in the range of 4-5.66 mcg daily, in women with body weight ≥80kg ; starting doses should be 4-6mcg daily. The doses should be titrated based on weight, previous response and ovarian reserve. For the first cycle lowest recommended dose should be selected..

Are intangible factors, such as stress, impacting miscarriage rates in IVF pregnancies during the COVID-19 pandemic?

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BACKGROUND AND OBJECTIVE

With the ongoing COVID-19 pandemic, it is clear that individuals have experienced more stress[1]. Research prior to COVID-19 has also linked higher stress levels to increased spontaneous miscarriage rates[2]. We hypothesized that intangible factors throughout the pandemic, such as stress, changes in disinfection protocols and possible asymptomatic COVID infections, could be associated with increased miscarriage risk in patients with IVF pregnancies during this time. A quality assurance (QA) study was conducted to monitor centre outcomes and hopefully provide valuable information to clinicians and patients.

MATERIALS AND METHODS

We conducted a retrospective quality assurance analysis with case-matched controls at a private fertility centre in British Columbia, Canada. IVF/ICSI cycles between April-December 2020 were compared with cycles from April 2018-March 2020 (pre-pandemic) to assess for differences in pregnancy and miscarriage rates.

This included fresh transfer cycles, frozen donor egg cycles, and frozen embryo transfer (FET) cycles (with and without pre-implantation genetic testing). The miscarriage rate was analyzed per pregnancy. Statistical analysis was performed by Student's t-test (continuous variables), and the Fisher's exact test (proportions).

TABLE 1

	Pre-Pandemic Period	Pandemic Period	Significance
Sample Size (Cycle Number)	Fresh IVF - 585 Frozen Oocyte IVF - 86 FET (no PGT-A) - 987 FET (PGT-A) - 194	Fresh IVF - 272 Frozen Oocyte IVF - 47 FET (no PGT-A) - 439 FET (PGT-A) – 96	
Mean Age (Years)	Fresh IVF – 36.3 Frozen Oocyte IVF – 41.5 FET (no PGT-A) – 36.2 FET (PGT-A) – 36.6	Fresh IVF – 35.8 Frozen Oocyte IVF – 40.6 FET (no PGT-A) – 36.0 FET (PGT-A) – 36.9	NS NS NS NS
Mean Number of Embryos Transferred	Fresh IVF – 1.54 Frozen Oocyte IVF – 1.10 FET (no PGT-A) – 1.29 FET (PGT-A) – 1.05	Fresh IVF – 1.36 Frozen Oocyte IVF – 1.09 FET (no PGT-A) – 1.26 FET (PGT-A) – 1.05	p<0.0001 NS NS NS

*NS = not significant

FIGURE 1

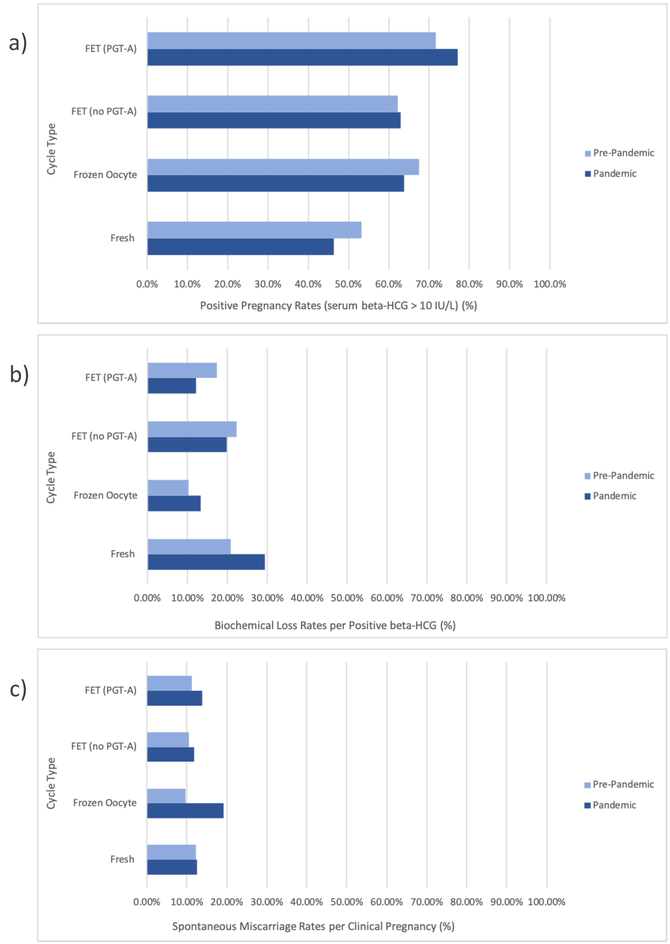

Figure 1. (a)Positive Pregnancy Rates Pre-Pandemic and During Pandemic, (b) Biochemical Loss Rates per positive b-HCG Pre- Pandemic and During Pandemic, (c) Spontaneous Miscarriage Rates per Clinical Pregnancy Pre-Pandemic and During Pandemic

RESULTS AND DISCUSSION

Nine months of IVF data from the start of the pandemic (854 cycles) was compared with the 24 months immediately preceding the pandemic (1852 cycles). Stratifying by cycle type, patient's ages were clinically similar between the two groups (Table 1).

A similar mean number of embryos was transferred in the frozen donor egg cycles, as well as the FET cycles (with and without PGT). Significantly fewer embryos were transferred in the fresh transfer group, 1.36 vs 1.54 ($p<0.0001$), which is likely reflective of a temporal change in practice, encouraging single embryo transfer.

Overall, no significant differences were seen in the clinical pregnancy rates between the pre-pandemic and pandemic pregnancy groups, nor in the biochemical loss rates per positive bHCG.

Across all treatment types, the spontaneous miscarriage rate per clinical pregnancy was not significantly higher during the COVID-19 pandemic.

CONCLUSION

Through this QA study, we can infer that the less tangible effects from the COVID- 19 pandemic, including changes in disinfection protocols affecting the baseline volatile organic compounds level, increased stress endured by patients, and possible asymptomatic COVID infection, do not appear to affect clinical pregnancy rates and miscarriage rates in IVF patients.

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Impact of age and fertility status on the consistency of repeat measurements of Sperm DNA Damage: A single-center, prospective, dual visit study

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Introduction and Aim

- The effect of age on male reproductive potential is not well defined
- Aging has been found to induce chromosomal anomalies, genetic mutations and epigenetic changes
- Sperm DNA damage is associated with a lower probability of conception
- We used Sperm Chromatin Structural Assay **(SCSA®)** to determine correlation between DNA damage with age and fertility status

Methods & Demographics

- Semen samples were obtained from 151 men aged 18-80 at two visits with one-to-three-month intervals
- Data were collected prospectively at our institution
- The participants were classified as infertile (n=69) and healthy fertile controls (n=82)
- Standard semen parameters were obtained
- SCSA® was done using a CytoFLEX Cytometer and analyzed using Winlist Software v8

Results

- %DFI groupings in this study were classified as: normal (<18%), intermediate (18-27%) and high (>27%)
- Data was analyzed in terms of three age groupings: <35, 35-49 and >50 years-old
- %DFI had the highest correlation between both visits (R=0.901) within all sperm parameters
- %DFI correlated positively with age (p<0.001)
- 48.6% of men with intermediate DFI changed category on the second visit (grey bar)

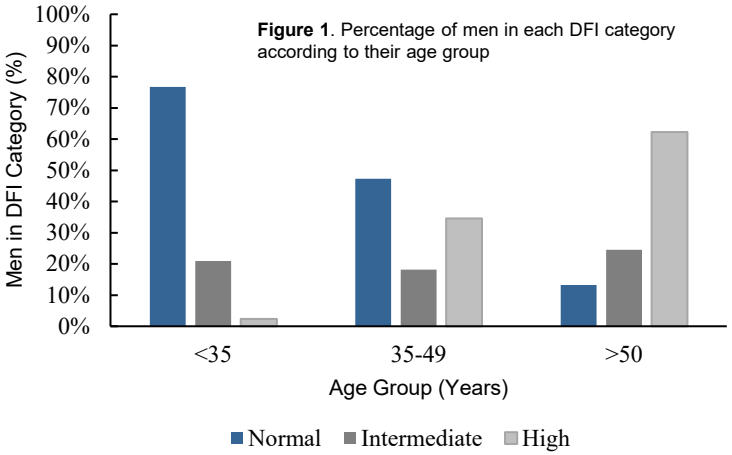

Figure 1. Percentage of men in each DFI category according to their age group

Table 1. Correlation analysis of the sperm parameters between visit 1 and visit 2

	[Sperm]	Progressive Motility	Total Motility	Avg DFI	Avg HDS
Spearman's Rho (P<0.001)	0.833	0.741	0.690	0.901	0.823

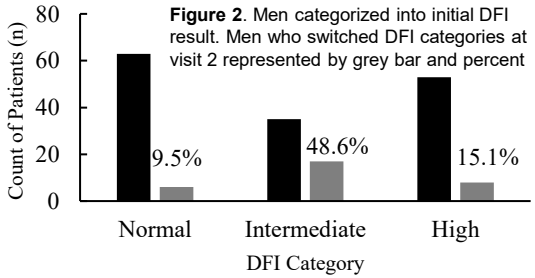

Figure 2. Men categorized into initial DFI result. Men who switched DFI categories at visit 2 represented by grey bar and percent

Discussion & Conclusion

- Advanced paternal age is correlated with increased DNA damage
- %DFI is a reliable and reproducible test
- Men with intermediate %DFI would benefit from repeat testing

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